Consumer and Corporate Affairs Canada
Consommation et Corporations Canada

(11) (A) No. 1 209 916

(45) ISSUED 860819

(52) CLASS 167-206
C.R. CL. 167-237

(51) INT. CL.[4] A61K 31/415,7/16

(19) (CA) **CANADIAN PATENT** (12)

(54) Antimycotic Agents in the Form of Gel Systems with High Release of Active Compound

(72) von Bittera, Miklos;
Hoff, Dieter;
Büchel, Karl H.;
Plempel, Manfred;
Regel, Erik,
Germany (Federal Republic of)

(73) Granted to Bayer Aktiengesellschaft
Germany (Federal Republic of)

(21) APPLICATION No. 441,948

(22) FILED 831125

(30) PRIORITY DATE Germany (Federal Republic of)
(P 32 44 027.8) 821127

No. OF CLAIMS 11 - NO DRAWING

Canada

DISTRIBUTED BY THE PATENT OFFICE, OTTAWA.
CCA-274 (11-82)

ABSTRACT OF THE DISCLOSURE

The invention provides for novel antimycotic agents in gel form for the treatment of fungal infections of the oral cavity. The gel form of the invention provides a depot effect, good adhesion properties and relatively high bioavailability of the active compounds. The gels of the invention make possible the use of short term therapy.

The present invention relates to novel gel formulations of the known antimycotic azole derivatives which show improved release of the active compounds and thus make short-term therapy possible.

Formulations of antimycotic derivatives for the treatment of mycoses in humans, especially mycoses of the skin, have already been disclosed. Using these formulations, a 14 to 21-day therapy period is necessary for complete healing.

In order to shorten the duration of therapy a certain depot effect and a greater bioavailability of the active compounds are necessary especially in order to eliminate the organisms and achieve mycological healing. The known formulations have only restricted suitability for this purpose because only a small proportion of the amount of active compound present dissolves in the volume of fluid at the site of infection. If it is now desired to shorten the duration of therapy by means of or without a further increase in the concentration of active compound, care must be taken that the bioavailability of the active compound is optimal.

It has now been found that those gel formulations of antimycotic azole derivatives which contain, in addition to customary formulating agents, 1-5% of benzyl alcohol and 2.5-35% of spreading agent and gel-forming agent release the active compound to a greater extent and thus permit shortening of the duration of therapy to 1 day. This effect of the improved release of active compound can extend up to a power of ten.

Thus, the present invention provides an antimycotic gel with improved release of the active compound, containing an antimycotic azole compound and customary formulation auxiliaries, characterised in that it contains 1-5% of benzyl

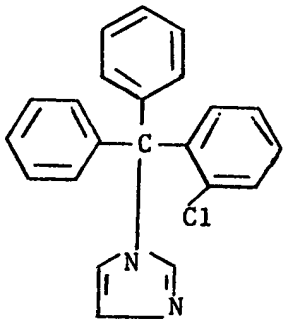
alcohol, 2.5-35% of spreading agent and, as the gel-forming agent, either

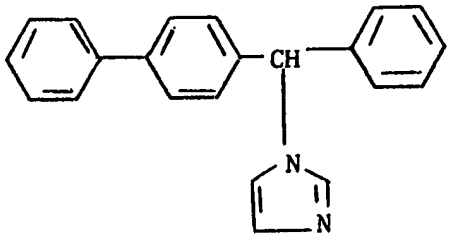
a) 10-30% of cetylstearyl alcohol oxyethylated with about 30 mols of ethylene oxide or

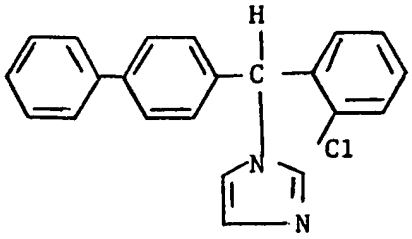
b) 1-5% of polyacrylic acid, polymethacrylic acid or a salt of polyacrylic acid or polymethacrylic acid.

Active compounds which can be formulated in this manner are any compounds having antimycotic activity, especially imidazole and triazole derivatives. They are present in the agents according to the invention in amounts preferably from 0.05% to 1%, most preferably 0.1 to 1%.

The compounds of the formulae below may be mentioned as examples:

I  clotrimazole

II  bifonazole

III  lombazole

Numerous other azole derivatives having antimycotic activity have been disclosed in DE-OS (German Published Specification) 2,430,039. They can likewise be used as active compounds in the agents according to the invention.

Spreading agents are understood as comprising oily liquids which distribute themselves particularly well on the skin. (R. Keymer, Pharm. Ind. 32 (1980), 577-581). The following compounds are especially suitable as spreading agents for the agents according to the invention:

Silicone oils of various viscosities.

Esters of fatty acids, such as ethyl stearate, di-n-butyl adipate, hexyl laurate, dipropylene glycol pelargonate, esters of a branched fatty acid of medium chain length with saturated C_{16}-C_{18} fatty alcohols, isopropyl myristate, isopropyl palmitate, esters of caprylic/capric acid with saturated fatty alcohols of chain length C_{12}-C_{18}, isopropyl stearate, isopropyl isostearate, oleyl oleate, decyl oleate, ethyl oleate, ethyl lactate, waxy esters of fatty acids, such as artificial duck preen gland fat, dibutyl phthalate, diisopropyl adipate, mixtures of esters related to the latter, polyol esters of fatty acids etc.

Triglycerides, such as caprylic/capric acid triglyceride, triglyceride mixtures with vegetable fatty acids of chain length C_8-C_{12} or other specially selected natural fatty acids, partial glyceride mixtures of saturated or unsaturated fatty acids which may possibly also contain hydroxyl groups, monoglycerides of C_8/C_{10} fatty acids etc.

Fatty alcohols, such as isotridecyl alcohol, 2-octyldodecanol, cetylstearyl alcohol and oleyl alcohol.

Fatty acids, such as, for example, oleic acid.

The following are spreading oils which are particularly well suited:

isopropyl myristate, isopropyl palmitate, esters of caprylic/capric acid with saturated fatty alcohols of chain length C_{12}-C_{18}, waxy fatty acid esters such as artificial duck preen gland fat, silicone oils, isopropyl myristate/isopropyl stearate/isopropyl palmitate mixture, isopropyl stearate and isopropyl isostearate.

The following additional auxiliaries and/or formulation base auxiliaries can be used in the production of the agents according to the invention: glycerol, high viscosity paraffin, low viscosity paraffin, triethanolamine, collagen, allantoin, novantisolic acid and perfume oils.

The gel-forming agent used is cetylstearyl alcohol with about 30 mols of ethylene oxide, optionally mixed with polyol esters of fatty acids, in concentrations of 10-30%.

Additional suitable gel-forming agents are those macromolecular compounds which can dissolve or swell in both water and organic solvents.

If a classification of macromolecular auxiliaries is followed (Keipert et al., Die Pharmazie 28, 145-183 (1973)), then, in particular, ionic macromolecules and their salt forms are used. These are, inter alia, polyacrylic acid, polymethacrylic acid and their salts,such as, for example, a slightly crosslinked polyacrylic acid of extremely high molecular weight which forms a clear gel structure by the addition of an alkali. In the cases of polymethacrylic acid and/or its salts, 1-5% is necessary.

Suitable solvents are water and all solvents which are miscible with water. Suitable examples are alkanols, such as ethanol and isopropyl alcohol, benzyl alcohol, propylene glycol, methylcellosolve, cellosolve, esters, morpholines, dioxane, dimethyl sulphoxide, dimethylformamide, tetrahydrofuran and cyclohexanone.

It is also possible to employ one or more solvents in the production of the formulations according to the invention.

The antimycotic gels according to the invention are prepared by a process in which a mixture including one or more antimycotic azole compounds 1 - 5% benzyl alcohol, 2.5 - 35% of spreading agent and, as a gel-forming agent, either

a) 10 - 30% of cetylstearyl alcohol oxyethylated with about 30 mols of ethylene oxide or

b) 1 - 5% of polyacrylic acid, polymethacrylic acid or a salt of polyacrylic acid or polymethacrylic acid

is melted at 110°C under a nitrogen atmosphere, combined with water and cooled down to 25° under slow stirring. The azole derivative is used preferably in an amount of 0.05 to 1%, most preferably of 0.1 - 1%.

The water phase consists of 35 - 55% demineralised water.

Example 1

Phase I	
Clotrimazole	1.000 g
Polyol esters of fatty acids	23.000 g
Cetylstearyl alcohol oxyethylated with about 30 mols of ethylene oxide	16.000 g
Isopropyl myristate	10.000 g
Benzyl alcohol	3.000 g

The mixture is heated to 100°C with stirring.

Phase II	
Demineralised water heated to 100°C	47.00 g

Phase II is slowly stirred into phase I at at least 95°C. Any loss of water is compensated for at 60°C and slow stirring is continued down to 50°C. The mixture is then cooled down from 50°C to 25°C without stirring (in order to

avoid inclusion of air and not adversely to affect the gel formation).

The procedure in Examples 2-6 is analogous.

Example 2

Bifonazole	1.00 g
Polyol esters of fatty acids	20.00 g
Cetylstearyl alcohol oxyethylated with about 30 mols of ethylene oxide	16.00 g
Isopropyl myristate	10.00 g
Benzyl alcohol	3.00 g
Lactic acid	1.50 g
Demineralised water	48.50 g

Example 3

Clotrimazole	1.00 g
Polyol esters of fatty acids	20.00 g
Cetylstearyl alcohol oxyethylated with about 30 mols of ethylene oxide	20.00 g
Isopropyl isostearate	5.00 g
96% strength ethanol	3.00 g
Benzyl alcohol	1.00 g
Demineralised water	50.00 g

Example 4

Bifonazole	1.00 g
Polyol esters of fatty acids	23.00 g
Cetylstearyl alcohol oxyethylated with about 30 mols of ethylene oxide	12.00 g
Isopropyl myristate	10.00 g
Benzyl alcohol	3.00 g
Demineralised water	51.00 g

Example 5

Lombazole	1.00 g
Polyol esters of fatty	20.00 g
Cetylstearyl alcohol oxyethylated with about 30 mols of ethylene oxide	20.00 g

Isopropyl isostearate	5.00 g
Ethanol	3.50 g
Benzyl alcohol	1.00 g
Demineralised water	49.50 g

Example 6

Bifonazole	1.00 g
Polyol esters of fatty acids	20.00 g
Cetylstearyl alcohol oxyethylated with about 30 mols of ethylene oxide	20.00 g
Isopropyl myristate	5.00 g
Benzyl alcohol	5.00 g
Demineralised water	49.00 g

Example 7

Phase I

Clotrimazole	1.00 g
dissolved in isopropanol	40.00 g

then the following are stirred in and dissolved

Polyol esters of fatty acids	4.00 g
Benzyl alcohol	3.00 g
Diisopropyl adipate	4.00 g

Phase II

Carbopol* 940 (a high polymer polyacrylate)	1.50 g
is introduced, with stirring into demineralised water	46.10 g
The mixture is allowed to swell for about 2h and neutralised with 45% strength NaOH	0.40 g

Phase I is slowly worked, in portions with stirring, into phase II.

The procedure in Examples 8 and 9 is analogous.

*Trade Mark

A

Example 8

Lombazole	1.00 g
Polyol esters of fatty acids	4.00 g
Isopropyl myristate	4.00 g
Benzyl alcohol	1.00 g
Isopropanol	45.00 g
Carbopol 940	1.50 g
45% strength NaOH	0.40 g
Demineralised water	43.10 g

Example 9

Bifonazole	1.00 g
Polyol esters of fatty acids	4.00 g
Isopropyl esters of coconut fatty acid	4.00 g
Benzyl alcohol	5.00 g
Isopropanol	45.00 g
Carbopol 940	1.50 g
45% strength NaOH	0.40 g
Demineralised water	39.10 g

Test of the efficacy of the agents according to the invention on guineapigs infected with trichophyton.

The test model which we used for the comparative test of the efficacy of the formulations according to the invention was Pirbrigth white guineapigs of average weight 600 g infected with trichophyton. The backs of the animals were shaved with an electric hair-cutting machine so that the remaining stubble was about 1/10 mm long.

The infection with Trichophyton mentagrophytes was carried out by gently rubbing a suspension of spores of the pathogen, which had been germinated in Sabouraud's nutrient solution for 24 hours, into an area of about 2 x 2 cm on the shaven backs of the animals. 0.5 ml of the suspension of organisms which contained $1 - 3 \times 10^5$ infectious fungal particles was applied to each animal.

Using this method of infection, the first symptoms of dermatophytosis appear 2 - 3 days after infection

as reddening and scaling of the skin. The dermatophytosis is maximal about 14 days after infection in untreated animals: areas of hair loss and haemorrhagic damage to the integument within a scaly edge zone with inflammatory changes.

The formulations to be tested were locally applied once, on the 2nd day after infection, to the reddened site of infection on the animals and gently rubbed in using a horn spatula.

In each case, 0.5 g of the formulations = 5 mg of active compound was applied. The course of infection was assessed each day up to the 20th day after infection.

The results of the tests can be seen in the table below.

Example of agent	Effect on guineapigs infected with trichophyton
1	****
2	****
3	****
3	****
5	****
6	****
7	****
8	****
9	****

****: very good effect
*** : good effect
**: effect
* : weak effect
0 : no effect

If, instead of the formulations according to the invention, formulations containing no benzyl alcohol and no spreading agent are used, an effect corresponding to that of the formulations according to the invention is only achieved after application three times.

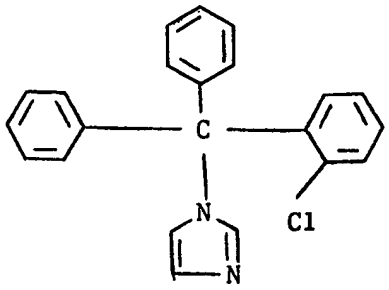
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. An antimycotic gel with improved release of the active compound, containing an antimycotic azole compound and customary formulation auxiliaries, characterised in that it contains 1-5% of benzyl alcohol, 2.5-35% of spreading agent and, as the gel-forming agent, either

a) 10-30% of cetylstearyl alcohol oxyethylated with about 30 mols of ethylene oxide or

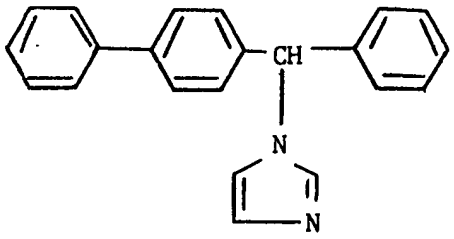
b) 1-5% of polyacrylic acid, polymethacrylic acid or a salt of polyacrylic acid or polymethacrylic acid.

2. An antimycotic gel according to Claim 1, characterised in that it contains clotrimazole of the formula



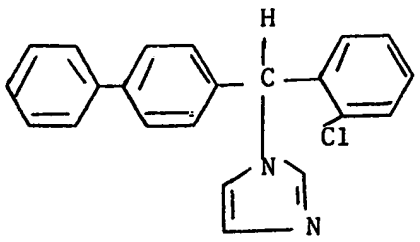
as the active compound.

3. An antimycotic gel according to Claim 1, characterised in that it contains bifonazole of the formula



as the active compound.

4. An antimycotic gel according to Claim 1, characterised in that it contains lombazole of the formula



as the active compound.

5. An antimycotic gel according to Claim 1, characterised in that it contains an antimycotic azole compound in an amount of 0.05-1%.

6. An antimycotic gel according to Claim 1, characterised in that it contains an antimycotic azole compound in an amount of 0.1-1%.

7. A process for the production of an antimycotic gel according to claim 1, characterized in that a mixture including one or more antimycotic azole compounds, 1-5% benzyl alcohol, 2.5-35% of spreading agent and, as a gel-forming agent, either

a) 10-30% of cetylstearyl alcohol with about 30 mols of ethylene oxide or

b) 1-5% of polyacrylic acid, polymethacrylic acid or a salt of polyacrylic acid or polymethacrylic acid is melted at 110°C under a nitrogen atmosphere, combined with water and cooled down to 25°C under slow stirring.

8. A process according to Claim 7, wherein the antimycotic compound is clotrimazole.

9. A process according to Claim 7 wherein the antimycotic compound is bifonazole.

10. A process according to Claim 7 wherein the antimycotic compound is lombazole.

11. A process according to Claim 8, 9 or 10 wherein the amount of antimycotic compound is 0.05-1%.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS

SUBSTITUTE

REMPLACEMENT

there are NO DRAWINGS

il n'y a PAS DE DESSINS